REMARKS

In the Office Action mailed October 3, 2007, a restriction of Applicant's invention was required as between:

Group I (Claims 1-13, 17, 22, 26-28, 30, 33-39, 43-44, and 52), drawn to a method of measuring forms of Factor XIIa *in a sample*;

Group II (Claims 1 and 57-69), drawn to methods of measuring forms of factor XIIa in a sample, wherein *the sample has been obtained from a subject having a disease or disorder*; and

Group III (Claims 70-91), drawn to a methods and databases for monitoring or diagnosing a disease or disorder via sample comparison to known subject data.

The Examiner reasoned as follows:

> "This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. To have a general inventive concept under PCT Rule 13.1, the inventions need to be linked by a special technical feature. The special technical feature that appears to link [the claims] is the measurement and differentiation of various forms of factor XIIa (FXIIa). The claims are also directed to the utility of the factor XIIa measurement in disease assessment. However, factor XIIa detection and differentiation has been taught by the prior art. For example, the reference to Esnouf et al. (Thromb Haemost 2000, Vol. 83, pages 874-881) discloses methods for detecting β-factor XIIa and α-factor XIIa with a monoclonal antibody designated mAb 2/215. See abstract. The procedures distinguish α-factor XIIa from the "α-factor XIIa:C1-INH complex" (other forms of factor XIIa). See page 877 – Results.
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> With respect to factor XIIa's use in disease, it is noted that both Dick et al. (Haemostasis, May 2000, Vol. 30, No. 1-2, page 92 – Abstract only) and Kariyawasam et al. (Journal of Hypertension, 2000, Vol. 18, No.Suppl.4 pages S24-S25 – Abstract only) teach factor XIIa measurements in renal and cardiovascular disorders.
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> Therefore the technical feature recited in claims 1-13 17, 22, 26-28, 30, 33-39, 43-44, 52, 57-70, 75, 77, 79-83, 88, and 90-91 is not a contribution over the prior art. Accordingly, the groups set forth below are no so linked as to form a single general concept under PCT Rule 13.1" (Office Action dated October 3, 2007, pages 2-3.)

Applicants traverse the restriction and request rejoinder of at least Groups I & II for the reasons set for below.

First, Applicant notes that the claims of invention Groups I & II do not set forth two inventions; rather, they represent *one method* wherein the particular *sample* to be used in the method is further defined in Claims 57-69, which claims have been arbitrarily assigned to Group II by the Examiner. That is, Claim 1 recites methods for detecting forms of activated Factor XII in a sample. Claim 57, which the Examiner characterizes as drawn to a separate invention, depends from Claim 1, and merely specifies that the *sample* is obtained from a subject having a disease or disorder. However, Applicant notes that Claims 10-12, which also specify the source of the sample, have been logically included in Group I. Accordingly, no basis is seen to exist to separate the claims of Group I from the claims of Group II.

Furthermore, it is noted that the claims of invention Group II all ultimately depend from the single method of Claim 1. Accordingly, the claims of Group II are *dependent* claims, and depend on the claims of Group I. PCT Rule 13.4 states:

> "*Dependent Claims*
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> Subject to Rule 13.1, it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention claimed in an independent claim, ***even where the features of any dependent claim could be considered as constituting in themselves an invention.***" (MPEP §1850, emphasis added)"

Additionally, the MPEP notes:

> "Although lack of unity of invention should certainly be raised in clear cases, ***it should neither be raised nor maintained on the basis of a narrow, literal or academic approach***....rigid rules cannot be given and each case should be considered on its merits, the ***benefit of any doubt being given to the applicant.***" MPEP §1850 (II).

Applicant submits that restricting claims which merely specify the source of the sample to be used in the claimed method is contrary to the international standards, and, at best, is arbitrary and academic, and therefore contrary to the MPEP regulations.

It is also noted that the Examiner asserts that the subject matter of the claims of Group I and II belong to different search classification groups (*i.e.*, Group I, drawn to a method of measuring forms of Factor XIIa *in a sample*, classified in class 435, subclass 7.1; Group II, drawn to methods of measuring forms of factor XIIa in a sample, wherein *the sample has been obtained from a subject having a disease*

or disorder, classified in class 424, subclass 146.1, and class 435, subclass 13). However, as noted in the MPEP, the Examiner:

> "should not raise objection of lack of unity of invention merely because the inventions claimed are classified in separate classification groups or merely for the purpose of restricting the international search to certain classification groups." MPEP 1850 (II)

Accordingly, because all of the claims of Group I and Group II are directed to *one method*, wherein the particular *sample* to be used in the method is further defined in Claims 57-69 (Group II), and in further view of the claims of Groups I & II ultimately depend from the method of Claim 1, Applicant submits that the claims of Group I & II relate to a single inventive concept, and a search of the art relevant to the Group I claims will reveal all the art relevant to the Group II claims, and vice versa. The claims are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted.

Esnouf et al.

The Examiner asserts that Esnouf et al., Thromb. Haemost., 83: 874-81 (2000) (hereinafter "Esnouf") describes the detection of forms of Factor XIIa, *i.e.*, α-factor XIIa and β-factor XIIa, and differentiation, *i.e.*, antibodies able to detect α-factor XIIa , but not able to detect α-factor XIIa complexed with the C1 esterase inhibitor, and therefore no special technical feature is seen to exist in the claims.

Applicants disagree. As taught by Applicant's specification, variation in forms of Factor XIIa reflecting the molecular weight and peptide chain sequence of the Factor XIIa result from progressive cleavage of the inactive zymogen Factor XII. Factor XII undergoes cleavage resulting in an 80Kd active serine proteinase, called Factor aXIIa that comprises a 52Kd heavy chain linked by a disulphide bond to a 28Kd light chain. Proteolysis of this factor releases a peptide from the heavy chain and results in a product, called Factor ßXIIa, which retains serine protease activity, but in which the 28Kd chain of aXIIa is disulphide linked to a small peptide fragment derived from the former 52Kd heavy chain. Factor ßXIIa can undergo further proteolytic cleavage resulting in a fragment with a molecular weight of approximately 15Kd, which has been designated by the Applicant as Factor ?XIIa.

Factor XIIa in any one of its variant forms, for example, as Factor aXIIa, ßXIIa or ?XIIa can associate with other molecular species, including high affinity binding partners, for example, inhibitors,

for example, C1 esterase inhibitor, and other binding proteins, for example, low affinity binding partners. It is postulated that association of Factor XIIa with such other binding proteins, for example, low affinity binding partners, may be reversible and may hinder binding to inhibitory proteins and hence reduce or prevent inhibition of Factor XIIa activity.

Factor XIIa in any one of its variant forms, for example, as Factor aXIIa, ßXIIa or ?XIIa may also associate with and dissociate from lipids, for example, lipoproteins, which may be in the form of particles and/or remnants of particles. Factor XIIa in any one of its variant forms, for example, as Factor aXIIa, ßXIIa or ?XIIa may associate with and dissociate from any of cells and cellular fragments. Particularly in the case of Factor XIIa associated with cells, cellular fragments, lipoproteins and lipoprotein remnants, several molecules of a form of Factor XIIa may be present on an individual particle. Furthermore, several molecules of Factor XIIa, either the same or different forms, may be present as a complex of Factor XIIa molecules.

Accordingly, it is clear that the present application is based on the realization that activated Factor XIIa exists *in vivo* in a large variety of different forms, and that the levels of these *in vivo* forms may be clinically significant.

In contrast, Esnouf teaches isolating *non-activated* Factor XII, which he then subjects to tryptic digest *in vitro* to obtain a-factor XIIa and ß-factor XIIa. The C1 esterase inhibitor/Factor XIIa complex was obtained by allowing the constituent proteins to associate *in vitro* as well. Esnouf then concludes that the monoclonal antibody mAb 2/215 bound *in vitro* prepared a-factor XIIa and ß-factor XIIa, but not Factor XII or a-factor XIIa:C1 esterase inhibitor complex. There is no teaching in Esnouf of the discovery that activated Factor XIIa exists *in vivo* in a large variety of different forms, or that the levels of these *in vivo* forms may be clinically significant.

Applicant has amended Claim 1 herein to specify a method for detecting or determining one or more forms of *in vivo* activated Factor XIIa in a sample, which comprises carrying out a procedure that is capable of detecting or determining the form or forms of Factor XIIa under investigation in preference to other forms of Factor XIIa. Support for the amendment is apparent throughout the specification, for example, page 14, line 30 through page 21, line 4.

Conclusion and Provisional Election

Applicants submit that in view of the foregoing amendments and remarks all the pending claims are seen to relate to a single inventive concept, and the claims are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted. Applicants request that the restriction requirement of the Office Action of October 3, 2007 be reconsidered and withdrawn, or, at least, the claims of Groups I & II be joined as one group.

Although, for reasons set forth above, Applicants believe that the restriction is improper and uncalled for, and without in any way acquiescing in the reasons for the requirements set forth in the Office Action, but in order to be fully responsive to the Office Action, Applicant elects Group I, drawn to a method of measuring forms of Factor XIIa in a sample, i.e., Claims 1-13, 17, 22, 26-28, 30, 33-39, 43-44, and 52.

Rejoinder

Applicant reminds the Examiner that restricted claims may be rejoined upon allowance of elected claims. The MPEP states:

> "If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. §§ 101 , 102 , 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04 (a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b)." MPEP § 1893.03(d)

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date

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